Effects of the Acyl Coenzyme A:Cholesterol Acyltransferase Inhibitor Avasimibe on Human Atherosclerotic Lesions

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Background—Inhibition of the acyl coenzyme A:cholesterol acyltransferase (ACAT) enzyme may prevent excess accumulation of cholesteryl esters in macrophages. The ACAT inhibitor avasimibe was shown to reduce experimental atherosclerosis. This study was designed to investigate the effects of avasimibe on human coronary atherosclerosis.

Methods and Results—This randomized, double-blind, placebo-controlled trial assessed the effects of avasimibe at dosages of 50, 250, and 750 mg QD on the progression of coronary atherosclerosis as assessed by intravascular ultrasound (IVUS). All patients received background lipid-lowering therapy if necessary to reach a target baseline LDL level <125 mg/dL (3.2 mmol/L). IVUS and coronary angiography were performed at baseline and repeated after up to 24 months of treatment. Approximately equal percentages of patients across groups received concurrent statin therapy (87% to 89%). The mean total plaque volume at baseline was 200 mm³, and the least squares mean change at end of treatment was 0.7 mm³ for placebo and 7.7, 4.1, and 4.8 mm³ for the avasimibe 50, 250, and 750 mg groups, respectively (adjusted \( P = 0.17 \) [unadjusted \( P = 0.057 \), 0.37, and 0.37, respectively]). Percent atheroma volume increased by 0.4% with placebo and by 0.7%, 0.8%, and 1.0% in the respective avasimibe groups (\( P = NS \)). LDL cholesterol increased during the study by 1.7% with placebo but by 7.8%, 9.1%, and 10.9% in the respective avasimibe groups (\( P < 0.05 \) in all groups).

Conclusions—Avasimibe did not favorably alter coronary atherosclerosis as assessed by IVUS. This ACAT inhibitor also caused a mild increase in LDL cholesterol. (Circulation. 2004;110:3372-3377.)

Key Words: atherosclerosis | ultrasounds | enzymes

Because rates of cardiovascular events remain unacceptably high despite the use of statins, a pharmacological intervention that would provide further protection is needed. The enzyme acyl coenzyme A:cholesterol acyltransferase (ACAT) has been an intriguing target for potential pharmacological intervention. ACAT is found in many tissue types that require the storage of cholesterol, including intestinal and hepatic tissue, as well as arterial macrophages. Cholesterol ester accumulation in macrophages indeed requires the action of ACAT, thereby promoting foam cell formation. The enzyme ACAT is also involved in the synthesis of cholesteryl esters packaged into VLDL by the liver. ACAT inhibitors have reduced cholesteryl esters and macrophage content and atherosclerotic lesions in the aorta and femoral arteries in preclinical studies. When administered with statins, the ACAT inhibitor avasimibe resulted in significant regression of previously established experimental atherosclerotic lesions. These antiatherosclerotic effects appeared to be independent of changes in plasma lipids. Clinical studies of avasimibe have demonstrated acceptable safety and tolerability when administered at daily doses up to 750 mg/d for up to 8 weeks. In patients with combined hyperlipidemia and hypoalphalipoproteinemia, avasimibe (250 to 750 mg/d) reduced plasma levels of triglycerides and VLDL cholesterol by up to 30%.

The primary objective of the Avasimibe and Progression of Lesions on UltraSound (A-PLUS) trial was to assess the effects of avasimibe on the progression of coronary atherosclerosis as assessed by intravascular ultrasound (IVUS). The hypothesis was that avasimibe would reduce atherosclerosis progression when administered with standard lipid-lowering therapy as needed.

Methods

Study Design and Population

A-PLUS was an international, multicenter, double-blind, placebo-controlled, randomized trial of 4 treatment groups: 50-mg, 250-mg, 750-mg, and placebo.
and 750-mg doses of avasimibe once daily versus placebo, plus usual care. The protocol was approved by institutional review boards. Patients ≥30 years of age referred for clinically indicated coronary angiography were evaluated before their scheduled procedures. Eligible patients provided written informed consent and medical history and underwent physical examination, electrocardiography, hematology, clinical biochemistry, and lipid profiles.

The study involved patients with chronic stable angina, or those who were post- or unstable angina, post-myocardial infarction, or post- percutaneous coronary intervention. To be eligible, patients needed to have at least one 20% to 50% diameter stenosis on angiography in 1 “target” coronary artery ≥2.5 mm in diameter. The target artery for IVUS was also required to not be influenced by prior or present percutaneous coronary intervention. Patients undergoing percutaneous coronary intervention in a non-target artery at the time of screening catheterization were included provided that the intervention was not considered at high risk of acute complications or restenosis. Additionally, patients needed to have reached an LDL cholesterol level ≤125 mg/dL (≤3.2 mmol/L) during the placebo-baseline period. Patients were excluded if they had previous coronary bypass surgery, severe left ventricular dysfunction (ejection fraction <25%), significant renal or hepatic dysfunction, uncontrolled hypertension, or diabetes with glycohemoglobin >10%. Serial coronary IVUS and angiographic studies were initially performed at baseline and after 24 months of therapy with avasimibe or placebo. Data emerged showing that pharmacological effects on atherosclerosis can be detected with IVUS in trials of shorter duration, the protocol was amended to obtain an average interval between both IVUS examinations of 18 months. This change required patients to reconsent in writing to continue in the study and complete their final visit procedures.

**IVUS and Coronary Angiography**

IVUS examinations were performed with the same system and with similar 30-MHz catheters at baseline and end of treatment. Intracoronary nitroglycerin (0.15 mg) was administered before the IVUS performed at baseline and at the end of treatment. The IVUS catheter was advanced into the target vessel ≥40 mm beyond the coronary artery ostium, to a recognizable landmark. IVUS images were recorded on S-VHS videotape as the IVUS transducer was pulled back automatically up to the guiding catheter by a motorized device (speed 0.5 mm/s). The baseline recording had to be judged acceptable by the IVUS core laboratory before the patient could enter the study. At follow-up, the IVUS catheter was placed in the same vessel imaged at baseline and positioned on the basis of original landmarks. These procedures helped to ensure that the coronary vessel was imaged consistently and that identical segments were analyzed at baseline and follow-up.

Identical conditions were maintained during the baseline and follow-up coronary angiography and included the intracoronary injection of nitroglycerin (0.15 mg) into each coronary artery. The segments of interest were visualized in multiple transverse and sagittal views to clearly separate stenoses from branches, minimize foreshortening, and obtain views as perpendicular as possible to the long axis of the segments to be analyzed.

**Image Analysis**

While examiners were blinded with regard to treatment assignment, all IVUS images were analyzed in the Montreal Heart Institute IVUS core laboratory by experienced technicians supervised by a cardiologist. The methods for analyses have been detailed previously and included side-by-side viewing of baseline and follow-up studies, review of landmarks and pullback speed, frame-by-frame comparison for matching segments, and digitization of images (15 digitized video frames/s). Distal and proximal branches were used as fiduciary sites to allow matching of the coronary segment to be traced. The lumen and external elastic membrane borders were manually traced on 1 of every 4 digitized cross sections with a custom-developed system (INDEC). Contours were interpolated for all the digitized cross sections between the manually drawn ones, but the segmentation was visually assessed in all cases on each cross section and always manually corrected if necessary. Interpolation of the lumen and external elastic membrane contours was performed according to an acoustic quantification method and a nonlinear algorithm, respectively, as described previously. A total of 900 cross sections were analyzed in the 30-mm segment of interest at both baseline and follow-up. Plaque, lumen, and total vessel volumes were computed for the entire length of the analyzed segments by multiplying the corresponding areas of each of the cross-sections by the distance between the neighboring slices and then adding all the products.

Because experimental data suggested that avasimibe may induce a more stable plaque composition, we performed an exploratory analysis of plaque characterization on both baseline and end-of-treatment IVUS examinations. A total of 6 matched-IVUS coronary segments were selected approximately at every 5 mm in the 30-mm segment. Every chosen cross section was divided into 5 regions, according to the types of plaque present: calcific, fibrotic, fibrohyaloechoic, hypoechoic, and normal. Fibrohyaloechoic plaque was defined as that which contained mixed hypoechoic and fibrotic signals in approximately equal quantities. The arc of each region was measured in degrees centered on the lumen, and the inner perimeter of each region was measured at the lumen-intima interface. Because of the multiple observations per patient (4 plaque types were available for each patient), the need to keep the patient as the unit of analysis, and the high correlation between plaque types (an increase in 1 arc type was always associated with a decrease in another arc type) that makes the statistical analysis more difficult to interpret, we calculated a single index per patient in light of the very good correlations between the 3 plaque types for matching the plaque types. The arc plaque characterization score and inner perimeter plaque characterization score were calculated for each cross section, by means of weighting factors:

\[
\text{arc score} = \left(0 \times \text{(normal)} + 1 \times \text{(hypoechoic)} + 1.5 \times \text{(fibrohyaloechoic)} + 2 \times \text{(fibrotic)} + 3 \times \text{(calcific)}\right) / \text{number of cross sections}
\]

The arc and inner-perimeter plaque characterization indexes were then created by summation of the respective characterization scores from each cross section, which was divided by the number of cross sections analyzed. An arc plaque characterization index of 0 would indicate a normal arterial wall, whereas an index of 3 would represent a cored vessel containing a calcified core.

The angiograms were viewed together and analyzed by means of the Cardiovascular Measurement System (MEDIS).

**Efficacy Parameters**

The primary outcome measure was the absolute change in plaque volume in a 30-mm segment of the target coronary artery assessed by 3D IVUS. Secondary efficacy parameters included the percent change in plaque volume and the change in percent atheroma volume in this 30-mm segment. The percent change in plaque volume was calculated as the absolute change divided by the baseline value, multiplied by 100. Percent atheroma (obstructive) volume was computed by dividing plaque volume by external elastic membrane volume and then multiplying by 100. The arc and inner-perimeter indexes were computed as exploratory end points, as described above. The change in angiographic coronary score was also calculated as the per-patient mean of the minimal lumen diameter changes for all lesions measured.

**Statistical Analysis**

Assuming an enrollment of 640 patients, a dropout rate of ~30%, and an SD of 30 mm³, the study had 80% power to detect an 11-mm³ difference in the primary end point with a 2-sided significance level of 0.05. The primary efficacy analysis was based on the intention-to-treat approach, which included all patients with baseline and follow-up IVUS data. The primary efficacy parameter, change in plaque volume in a 30-mm segment of the target coronary artery assessed by 3D IVUS was analyzed by means of an ANCOVA...
model, with treatment, center, and interval time as effects and the baseline measure as a covariate. Secondary parameters for changes from baseline were analyzed in a manner similar to the primary efficacy parameter. All analyses were done with a 2-sided significance level of 5%. Adjustments to probability values were based on Hochberg’s method for multiple comparisons for the assessment of plaque volume.

### Results

There were 639 patients randomized at 27 centers located in Canada, the United States, Europe, Australia, and South Africa. There were no significant differences in baseline characteristics among groups (Table 1). Statins were used by 65% of patients at screening, and mean LDL cholesterol was 89 to 93 mg/dL before randomization. Approximately equal percentages of patients across groups received concurrent statin therapy during the study (87% for placebo and 87%, 88%, and 89% for the avasimibe 50-, 250-, and 750-mg groups, respectively). One hundred thirty patients withdrew during double-blind treatment, with comparable numbers withdrawing from the placebo (35 patients) and avasimibe (31, 37, and 27 patients for 50, 250, and 750 mg) groups. A total of 509 patients completed the double-blind phase: 119 in the placebo group and 126, 127, and 137 in the avasimibe groups (31, 37, and 27 patients for 50, 250, and 750 mg) groups. A total of 77 patients (10 in the placebo group and 18, 29, and 20 in the 3 avasimibe groups) had IVUS studies that were not obtained at follow-up or were not analyzable. The mean time between baseline and follow-up IVUS measurements was 18 months in all groups.

### IVUS and Angiographic Results

The mean total plaque volume was $\approx 200$ mm$^3$ at baseline in all study groups (Table 2). The least squares mean change in plaque volume at end of treatment was 0.7 mm$^3$ for placebo, and 7.7, 4.1 and 4.8 mm$^3$ for the avasimibe 50, 250 and 750 mg groups respectively (adjusted probability values =0.17 (unadjusted $P=0.057$), 0.37 and 0.37). The least squares mean percent change in plaque volume was 1.5% in the placebo group and 4.9%, 2.6%, and 2.5% in the respective avasimibe groups (adjusted $P=0.16$, unadjusted $P=0.05$, for 50 mg versus placebo). Percent atheroma volume increased by 0.4% with placebo and by 0.7%, 0.8%, and 1.0% in the respective avasimibe groups ($P=NS$).

The arc index increased from baseline to end of treatment by 0.0432 in the placebo group and by 0.0372, 0.0339, and 0.0128 in the avasimibe 50-, 250-, and 750-mg groups, respectively ($P=0.012$ for avasimibe 750 mg versus placebo; Table 3). The angiographic coronary score decreased at end of treatment by 0.03 mm in the placebo group and by 0.07, 0.03, and 0.07 mm in the respective avasimibe groups ($P=NS$).

### Plasma Biomarkers

LDL cholesterol increased during the study by 1.7% with placebo but by 7.8%, 9.1%, and 10.9% in the respective avasimibe groups ($P<0.05$ in all avasimibe groups). Avasimibe 750 mg also induced significant reductions in triglycerides and apolipoprotein (apo) B compared with placebo ($P\leq0.01$). There was no effect of avasimibe at any dose on high-sensitivity C-reactive protein (Table 4).

### Adverse Events

Avasimibe was well tolerated at all dosages (Table 5). There were a total of 12 deaths during the study, with a rate of 1.9% in the placebo and the combined avasimibe groups. None of the deaths were associated with the study medication.

### Discussion

In this international, multicenter, randomized clinical trial, avasimibe did not favorably influence coronary atherosclero-
Avasimibe is an ACAT inhibitor that has demonstrated antiatherosclerotic activity in terms of reduced lesion size and morphological changes in various animal models.10–13 Studies suggested the potential antiatherosclerotic benefit associated with the inhibition of ACAT-1 present in macrophages.7,10,12 ACAT-1 is believed to play an important role in differentiating monocytes and in forming foam cells during atherosclerosis as assessed by IVUS. The increase in plaque burden over the study course tended to be modestly greater in the avasimibe groups than with placebo. Although avasimibe induced dose-related reductions in plasma triglycerides by up to 16%, LDL cholesterol increased by 8% to 11% in the placebo and 5% to 16% in the avasimibe groups than with placebo. Although avasimibe appeared to be independent of lipid changes.10–12 These studies suggested the potential antiatherosclerotic benefit associated with the inhibition of ACAT-1 present in macrophages.7,10,12 ACAT-1 is believed to play an important role in differentiating monocytes and in forming foam cells during atherosclerosis as assessed by IVUS. The increase in plaque burden over the study course tended to be modestly greater in the avasimibe groups than with placebo. Although avasimibe induced dose-related reductions in plasma triglycerides by up to 16%, LDL cholesterol increased by 8% to 11% in the actively treated arms.

Avasimibe is an ACAT inhibitor that has demonstrated beneficial effects on plasma lipid levels and direct antiatherosclerotic activity in terms of reduced lesion size and morphological changes in various animal models.10–13 Studies suggested the potential antiatherosclerotic benefit associated with the inhibition of ACAT-1 present in macrophages.7,10,12 ACAT-1 is believed to play an important role in differentiating monocytes and in forming foam cells during atherosclerosis as assessed by IVUS. The increase in plaque burden over the study course tended to be modestly greater in the avasimibe groups than with placebo. Although avasimibe induced dose-related reductions in plasma triglycerides by up to 16%, LDL cholesterol increased by 8% to 11% in the actively treated arms.

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### TABLE 2. IVUS Results

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=109)</th>
<th>Avasimibe 50 mg (n=108)</th>
<th>Avasimibe 250 mg (n=98)</th>
<th>Avasimibe 750 mg (n=117)</th>
<th>Avasimibe, All (n=323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total plaque volume, mm³</td>
<td>202.4±74.7</td>
<td>191.9±67.7</td>
<td>200.0±69.5</td>
<td>202.3±72.8</td>
<td>198.2±70.1</td>
</tr>
<tr>
<td>Mean change±SD</td>
<td>79.9±69.8</td>
<td>192.1±67.9</td>
<td>200.2±68.3</td>
<td>204.3±80.2</td>
<td>200.9±73.1</td>
</tr>
<tr>
<td>Percent change in plaque volume</td>
<td>25±26.6</td>
<td>5.1±30.0</td>
<td>1.2±24.2</td>
<td>1.9±33.1</td>
<td>2.8±29.5</td>
</tr>
<tr>
<td>Unadjusted P value</td>
<td>0.058</td>
<td>0.37</td>
<td>0.25</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Adjusted P value†</td>
<td>0.17</td>
<td>0.37</td>
<td>0.37</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Change in percent atheroma volume, %</td>
<td>3.6±12.7</td>
<td>1.2±12.8</td>
<td>1.0±14.7</td>
<td>1.9±14.6</td>
<td></td>
</tr>
<tr>
<td>Unadjusted P value</td>
<td>0.053</td>
<td>0.52</td>
<td>0.56</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Adjusted P value†</td>
<td>0.16</td>
<td>0.56</td>
<td>0.56</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

LS indicates least squares; NA, not applicable.

*Least squares mean change from baseline to final value based on ANCOVA model with treatment, center, and interval time as effects and baseline value as covariate.

†Adjusted P value based on Hochberg’s multiple comparisons procedure for the 3 pairwise comparisons vs placebo.

### TABLE 3. IVUS Assessment of Plaque Characterization Indexes

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Avasimibe 50 mg</th>
<th>Avasimibe 250 mg</th>
<th>Avasimibe 750 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arc index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean (SE)</td>
<td>1.2190</td>
<td>1.1248 (0.0330)</td>
<td>1.1859 (0.0359)</td>
<td>1.1547 (0.0364)</td>
</tr>
<tr>
<td>End-of-study mean (SE)</td>
<td>1.2578</td>
<td>1.1588 (0.0345)</td>
<td>1.2158 (0.0378)</td>
<td>1.1649 (0.0360)</td>
</tr>
<tr>
<td>LS mean change* (SE)</td>
<td>0.0432</td>
<td>0.0372 (0.0091)</td>
<td>0.0339 (0.0094)</td>
<td>0.0128 (0.0086)</td>
</tr>
<tr>
<td>P value</td>
<td>...</td>
<td>0.63</td>
<td>0.46</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Inner-perimeter index

| Baseline mean (SE)     | 1.2074  | 1.1160 (0.0330) | 1.1739 (0.0358) | 1.1452 (0.0362) |
| End-of-study mean (SE) | 1.2463  | 1.1484 (0.0349) | 1.2031 (0.0378) | 1.1555 (0.0359) |
| LS mean change* (SE)  | 0.0429  | 0.0353 (0.0092) | 0.0328 (0.0095) | 0.0125 (0.0087) |
| P value                | ...     | 0.54           | 0.43           | 0.013           |

LS indicates least squares.

*Least squares mean change from baseline to final value based on ANCOVA model with treatment, center, and interval time as effects and baseline value as covariate.
simibe has also been shown to induce cytochrome P450
3A4 activity and reduce plasma levels of different con-
comitant medications.29 Because 88% of patients were
-treated with HMG-CoA reductase inhibitors in A-PLUS,
the increases of up to 11% in LDL cholesterol observed
with avasimibe in the present study may therefore be
explained both by inhibition of ACAT-2 and a pharma-
cookinetic interaction with statins. Avasimibe also reduced
plasma apoB levels by 20% in A-PLUS when given at a
dose of 750 mg. This finding is in agreement with animal
studies showing that ACAT inhibition decreases apoB
secretion by a mechanism that involves enhanced intracel-
ular degradation of apoB.8,10,26

There were trends for a modest increase in atherosclerotic
burden in patients taking avasimibe in the present study. The
increases were not statistically significant and may be related
to the play of chance. Nonetheless, it is noteworthy that a
mild increase in LDL cholesterol occurred during avasimibe
treatment. The 7.8%, 9.1%, and 10.9% increases in LDL
cholesterol in the avasimibe 50-, 250-, and 750-mg groups
were paralleled with trends for mean increases in percent
obstructive volume of 0.7%, 0.8%, and 1.0%, respectively.
Whether these parallel changes were causally associated is
unknown; however, it underscores the potential importance of
even small changes in LDL cholesterol in patients with
coronary artery disease and the potential detrimental effects
of increases in unesterified cholesterol in the arterial wall
associated with ACAT inhibition.27,28 The increase over the
study course in plaque characterization indexes or overall
echogenicity was also significantly less marked with ava-
simibe than in the placebo group, which may indicate a
reduced tendency to plaque fibrosis in the actively treated
groups. Whether the absence of beneficial effects on athero-
sclerosis is specific to avasimibe, related to inhibition of both
ACAT-1 and ACAT-2 and pharmacokinetic interaction with
statins, or common to all ACAT inhibitors is presently
unknown. Clinical trials with other ACAT inhibitors using
atherosclerosis imaging29 will be necessary to address this
important clinical question.

In conclusion, avasimibe does not favorably alter coronary
atherosclerosis as assessed by IVUS. The observed changes
in plasma lipids, including a mild increase in LDL cholester-
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Acknowledgments
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### TABLE 4. Changes in Plasma Biomarkers*

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Placebo</th>
<th>50 mg</th>
<th>250 mg</th>
<th>750 mg</th>
<th>50 mg</th>
<th>250 mg</th>
<th>750 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C, %</td>
<td>17 (2.2)</td>
<td>7.8 (2.2)</td>
<td>9.1 (2.1)</td>
<td>10.9 (2.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>-1.0 (1.3)</td>
<td>0.8 (1.3)</td>
<td>1.2 (1.3)</td>
<td>2.3 (1.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoB, %</td>
<td>-4.0 (4.6)</td>
<td>-2.6 (4.5)</td>
<td>-10.4 (4.5)</td>
<td>-20.0 (4.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hs-CRP (log)†</td>
<td>0.049 (0.084)</td>
<td>0.091 (0.083)</td>
<td>0.16 (0.082)</td>
<td>0.000 (0.079)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG, %</td>
<td>1.8 (3.3)</td>
<td>-6.0 (3.3)</td>
<td>-7.7 (3.2)</td>
<td>-15.8 (3.2)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
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| ALT/AST       | 3376 Circulation November 23, 2004

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### TABLE 5. Safety Evaluation

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo</th>
<th>50 mg</th>
<th>250 mg</th>
<th>750 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>2 (1.3)</td>
<td>3 (1.9)</td>
<td>3 (1.8)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>CK ≥3×ULN</td>
<td>3 (1.9)</td>
<td>3 (1.9)</td>
<td>2 (1.2)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>ALT/AST ≥3×ULN</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (3.7)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

Values are n (%).

*None of the deaths were associated with study medication.
Francine Duval, Ginette Grenier, and Colombe Roy). We also sincerely thank all the A-PLUS investigators and coordinators.

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Effects of the Acyl Coenzyme A:Cholesterol Acyltransferase Inhibitor Avasimibe on Human Atherosclerotic Lesions

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for the Avasimibe and Progression of Lesions on UltraSound (A-PLUS) Investigators

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